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A multi-dataset time-reversal approach to clinical trial placebo response and the relationship to natural variability in epilepsy

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ABSTRACT

Purpose: Clinical epilepsy drug trials have been measuring increasingly high placebo response rates, up to 40%. This study was designed to examine the relationship between the natural variability in epilepsy, and the placebo response seen in trials. We tested the hypothesis that 'reversing' trial direction, with the baseline period as the treatment observation phase, would reveal effects of natural variability.
Method: Clinical trial simulations were run with time running forward and in reverse. Data sources were: SeizureTracker.com (patient reported diaries), a randomized sham-controlled TMS trial, and chronically implanted intracranial EEG electrodes. Outcomes were 50%-responder rates (RR50) and median percentage change (MPC).
Results: The RR50 results showed evidence that temporal reversal does not prevent large responder rates across datasets. The MPC results negative in the TMS dataset, and positive in the other two.
Conclusions: Typical RR50s of clinical trials can be reproduced using the natural variability of epilepsy as a substrate across multiple datasets. Therefore, the placebo response in epilepsy clinical trials may be attributable almost entirely to this variability, rather than the "placebo effect".
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1. Background

Nearly 1 out of 3 of patients with epilepsy do not yet have control over their seizures [1], and face 1.6-3 fold increase in mortality compared to the general population [2]. In spite of this, there has been great difficulty in providing patients new treatments that can improve seizure control. One significant challenge has been financial; clinical trials are increasingly expensive [3], and the risk of conducting a trial that fails to show superiority over placebo is a significant concern. This is compounded by the increasing placebo response rates over recent decades [4]. Thus, finding ways to reduce the placebo response can help contain costs for clinical trials, and in turn accelerate development of new therapies for epilepsy.

The term "placebo response" is used here to capture the effect size measured in the placebo arm of a clinical trial. The "placebo effect" for our purposes is defined as a measureable effect relevant to the disease that is directly attributable to the placebo given during the trial [5,6]. The placebo response has been thought to comprise a number of unrelated causes, principally: (A) psychological factors [7–16], (B) regression-to-the-mean [17] and (C) natural variability of disease [8]. Psychological causes include the "placebo effect", classical conditioning, the Hawthorne effect, symbols and expectations, and social learning. Regression-to-the-mean for our purposes refers to the impact of patients who are sicker than their usual registering for a trial. Such patients are expected to subsequently return to their "average disease" state without any intervention. Both regression-to-the-mean and psychological causes produce an improvement in disease. Natural variability in the context of epilepsy trials relates to the expected variation in seizure frequency over time, even in the absence of a change in treatment. Although these causes have been well described for many years, no study has attempted to dissect the relative contribution of each in epilepsy trials. Yet the time-course of these causes is expected to differ significantly. Psychological

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effects would be expected to occur after placebo administration and gradually wear off [18], regression to the mean would be expected to occur prior to placebo administration and continue afterwards, and natural variability would show no clear pattern before or after placebo administration. Moreover, if one reversed the direction of time, the first two of these effects would exhibit minimal responder rates, while the third may result in similar rates as the forward direction. Of note, the reverse temporal responder rate is not predictable given the traditional responder rate, because different baselines are used, and they represent different fractions of the overall trial population.

Recently, our group reported preliminary evidence that placebo response may simply reflect natural variability in epilepsy [19]. Based on that observation, we sought to validate this claim using several data sources that range from one of the world's largest patient-managed seizure diary database (SeizureTracker.com) [19,20], and a transcranial magnetic stimulation (TMS) clinical trial [21], to one of the world's most accurate seizure diary dataset based on longitudinal intracranial monitoring (NeuroVista data) [22]. We tested the hypothesis that 'reversing' trial direction, with the baseline period as the treatment observation phase, would show large and roughly similar responder rates to 'forward' trial analysis due to natural variability (Fig. 1).

2. Methods

2.1. Artificial simulation

To illustrate the key concepts being tested, 3 artificial datasets were constructed: (A) "psychological effects", (B) "regression-to-the-mean", and (C) "natural variability" (Fig. 2). In each, 150 simulated patient diaries (5 entries per patient) were generated with random number generators to represent 5 months. In all cases, the patient's "usual" monthly seizure rate was 15. For all three, zero-mean normally distributed noise was added (A: std. dev. = 8, B: std. dev. = 8, C: std. dev = 10). There was more variability in the random noise added to C intentionally. For A, each patient had the following added to their 5 diary entries: 0, 0, −8, −7, −3. For B, each patient had the following added to their diary entries: 8, 6, 2, 0, 0. For C, nothing was added to the diary values. These artificial sets of patients were analyzed in the forward and reverse time analysis of 50% responder rate, in order to demonstrate the pattern expected depending on the cause of placebo response.

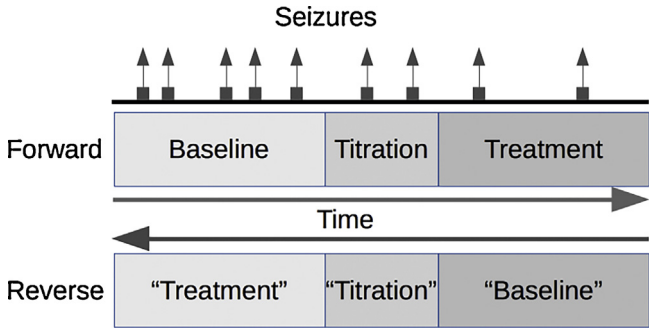

Fig. 1. Time reversal. A model for calculating outcomes from a clinical trial in forward and reverse direction. Small vertical arrows represent seizures times. Baseline and treatment periods can be redefined for "reverse" calculation of effect. In this hypothetical patient example, there are 5 seizures shown in the baseline period, 2 seizures during titration and 2 during treatment. For this illustration, we assume an 8-week baseline, 4-week titration, and 8-week treatment period. The percentage change for this patient is therefore 60% (using (5–2)/5). In the reverse direction, the patient has a negative 50% change (using (2–5)/2). Thus, in the forward calculation, this patient would be a 50%-responder, but not so in the reverse calculation.

2.2. General simulation technique with realistic data

For each of the datasets, a common simulation framework was used. A trial-sized segment of with 8 weeks of baseline and 8 weeks of treatment was used from the start of each patient's diary. A "titration period" was included merely to be more clinically realistic. In the case of SeizureTracker and NeuroVista, a 4-week "titration" period was inserted in between the two. In the TMS study, the structure of the study included a 2-week intervention period, roughly analogous to the 4-week titration period. For all datasets, patients were only included if they had $\geq$8 seizures during the baseline period (i.e. at least 1 seizure per week on average). Data were then analyzed for 2 outcomes, 50%-responder rate (RR50) and median% seizure frequency change (MPC). RR50 represented the proportion of patients that had a 50% or larger reduction in 28-day seizure rate during the intervention period compared with their baseline. MPC represented the median (across patients) % change in 28-day seizure rate between baseline and intervention. When time flowed in the forward direction, this was referred to as "forward." All patients' seizure diaries were then temporally reversed, such that the final day became the first day, and the first day became the last, and so forth (Fig. 1). When analyzing the reverse temporal flow, the eligibility criteria were re-applied. RR50 and MPC were then calculated on these reversed diaries, referred to as "reverse."

We introduce a metric, τ, for determining if temporal reversal appears to matter. For the RR50 rate in the forward direction denoted F, and the RR50 rate in the reverse direction denoted R:

$$\tau = \frac{2R - F}{F} \quad (1)$$

If $\tau \geq 0$, the relative contribution of natural variability to placebo response could be said to be large, whereas if $\tau < 0$, then it could be small (compared to other influences). The methodology for calculating p-values is described in the Appendix.

2.3. SeizureTracker based realistic simulation

SeizureTracker is a free online and mobile patient reported database of seizure diaries [20]. Data was exported from December 2007 through May 2016. Of note, this represents an expanded set of data compared with that originally studied previously [19], adding an additional 2 years. Patients with no seizures, no age reported, or absurd ages (i.e. >200 years old) were excluded. Seizures with invalid dates or identically repeated records were excluded.

All SeizureTracker simulations began with time zero representing the first recorded seizure in an individual's diary [19]. For each simulation, eligibility criteria were applied in the forward direction and patients were selected. To be eligible, patients needed on average at least 1 seizure per week during the baseline period [21]. Selected patients were then enrolled in a simulated clinical trial lasting 5 months (2-month baseline, 1-month titration, and a 2-month treatment period), to match typical modern clinical trials [23]. The outcome measures of RR50 and MPC in 28-day seizure frequency were calculated in the typical fashion using the baseline and treatment periods. The same patients' diaries were then reversed temporally, such that the last moment of the trial became the first, and the first moment became the last. A special requirement was imposed only in the SeizureTracker dataset that any patient who became "seizure-free" during the treatment period was not included in final calculations. This was done to avoid the possibility of including patients with "diary fatigue," i.e. patients who simply stopped recording events partway through the diary.

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